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Summary of the risk management plan (RMP) for Ionsys (fentanyl)

This is a summary of the risk management plan (RMP) for Ionsys, which details the measures to be taken in order to ensure that Ionsys is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Ionsys, which can be found on Ionsys' EPAR page.

Overview of disease epidemiology

Ionsys (fentanyl) is used to control moderate to severe pain after an operation in adults who are in hospital.

Short-term pain following surgery is common. In 2004, approximately 2.7 million adults were treated for this type of pain in France, Germany, Italy, Spain, and the UK. An estimated 234 million major surgeries are performed worldwide each year, with up to 75% of patients experiencing post-surgical pain.

Summary of treatment benefits

Ionsys is a transdermal system that delivers the active substance, fentanyl, through the skin. Fentanyl is an opioid that has been used to control pain for many years. When in pain, the patient uses a button on the Ionsys system to start the delivery of a dose of fentanyl.

Ionsys has been shown to be effective at controlling pain after an operation in seven main studies involving a total of around 3,300 patients. In three of the studies, Ionsys was compared with placebo (a dummy system). The proportion of patients who stopped treatment because their pain was not controlled was lower in patients treated with Ionsys (and ranged between 8% and 27%) than in those treated with placebo (where it ranged between 40 and 57%).

The other four studies compared Ionsys with morphine given by injection into a vein, and looked at the number of patients who judged their pain relief as 'good' or 'excellent'. These studies showed that Ionsys is as at least as effective as morphine at controlling pain.

All the studies described above were carried out with a different delivery device, which was recalled from the market in 2008 because of a defect in the design of the system. The defect has been corrected in the new system.

Unknowns relating to treatment benefits

Ionsys was evaluated in a large clinical programme. Elderly patients, obese patients, and patients of different races were well represented in the studies. There is no evidence to suggest that results would be different in other groups of patients.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Misuse/ abuse/ diversion/ addiction and dependence	It is known that fentanyl (the active substance in Ionsys) has been abused or misused by some patients. Tampering with Ionsys when it is being used may cause serious harm or even death.	Ionsys can only be used in hospital settings where treatment should be monitored by a healthcare professional experienced in the use of opioids such as fentanyl. Due to the potential of abuse with fentanyl, the doctor should evaluate whether the patient has a history of drug abuse before giving Ionsys and if so follow the patient closely. Ionsys is to be removed prior to leaving the hospital.
Medication errors (including accidental exposure)	Potential medication errors include allowing someone who is not the patient to press the dosing button, which could cause overdose, as well as accidental exposure. There is also potential for accidental exposure to fentanyl in the Ionsys system by both healthcare professionals and patients.	The prescribing information of Ionsys provides clear instructions regarding the handling and use of the transdermal system. Healthcare professionals will also be provided with a checklist to help prevent and minimise the occurrence of medication errors such as errors due to tampering and to remind patients that no one else other than them should press the button on the Ionsys system. To prevent and minimise accidental exposure, treatment with Ionsys should be supervised by a healthcare professional.
Difficulty breathing (respiratory depression)	Slowing of breathing is the most serious complication of opioid treatment. Some patients may also experience sleepiness.	Patients should be closely monitored for signs and symptoms of respiratory depression. No one other than the patient should press the Ionsys dosing button.
Overdose	A high dose or an overdose of fentanyl can have serious consequences for the patient's health. For example, an overdose could reduce the rate of breathing or even stop breathing altogether.	The following instructions should be followed to prevent overdose: • The dosing button should never be pressed by anyone other than the patient. • The patient must be instructed that Ionsys may not be used by or shared with others. • Any accidental contact should be treated by rinsing the affected area with water only (not soap). • Gloves must be worn when handling

Risk	What is known	Preventability
		Ionsys during assembly, application, removal and disposal. • Patients should also be assessed for signs of fentanyl overdose during Ionsys treatment.
Interactions with other medicines	Use of Ionsys with antidepressants may result in slowed breathing, low blood pressure, and significant sleepiness and progression to coma. Use of Ionsys with medicines known as CYP3A4 inhibitors such as ritonavir may result in a higher than normal fentanyl blood level. This in turn can increase the risk of side effects such as slowed breathing. Use of Ionsys with other medicines called SSRIs (selective serotonin re-uptake inhibitors), SNRIs (serotonin norepinephrine re-uptake inhibitors), or MAOIs (monoamine oxidase inhibitors) may cause a potentially life-threatening illness called serotonin syndrome.	The prescribing information for Ionsys provides detailed information on the potential for interactions of Ionsys with other medicines. To minimise the risks of interactions, the use of Ionsys is restricted to hospitals, where healthcare professionals are aware of all concomitant medications the patient is taking.
Skin reaction where the product was applied (application-site reactions)	The gel inside the system may be irritating to the skin.	Removing the Ionsys system after 24 hours of use and changing the application site may prevent skin irritation.

Important potential risks

Risk	What is known
Device not working correctly or at all (device malfunction/failure, including use during MRI, cardioversion, or defibrillation)	A device not working will cause the system to turn off permanently. Attempts to continue using the system will not produce any doses and pain may worsen. Ionsys requires successful attachment of two pieces: the controller and a drug unit. Failure to properly put the system together could cause the system not to work. Exposure to strong electromagnetic fields (e.g. from MRI or defibrillation) could cause the system not to work and turn off permanently.
Inadequate product	The system must be first put together for use and then applied to the patient.

Risk	What is known
disposal	The system must be safely removed after use and thrown away. Accidental contact of the healthcare professional, other hospital staff, and visitors (including children) can occur if the used system is not thrown away according to the disposal instructions. Contact with the medicine gel can result in significant health problems.
Use of the product outside its approved use (off-label use)	Off-label use of Ionsys may cover use in unapproved types of pain, use in adolescents, and use for a prolonged duration. There is also a potential for off-label use of Ionsys outside the well-monitored environment of a hospital.
Use in patients with hearing impairment	The system provides noise and light alert signals. Patients with hearing problems may not hear the noise signals from the system. In addition, these patients may not be aware of a system not working and not know that the system no longer gives medicine when the dose button is pressed. This may cause a lack of pain control.

Missing information

Risk	What is known
Use in pregnancy or breastfeeding	There is not enough information on the use of fentanyl or Ionsys in pregnant women. Patients must tell their doctor before using Ionsys if they are pregnant, may be pregnant, or are planning to become pregnant. The doctor will discuss the possible risks and potential benefits of using Ionsys. Ionsys should not be administered during childbirth, because fentanyl crosses the placenta. If Ionsys is given during childbirth the baby may need to be given an antidote when born. Prolonged treatment with fentanyl may cause withdrawal symptoms in the newborn baby. Fentanyl can pass into breast milk and may cause side effects in the breastfed child. The patient should not start breastfeeding until the Ionsys system has been removed for 24 hours.
Use in children (paediatric use)	The clinical studies focused primarily on short-term pain in adult patients after surgery. Only 124 children (aged 5 to 16 years) were involved in these studies. The small size of this group is not enough to guide safe and effective dosing in patients less than 18 years of age.
Use in patients with liver problems (hepatic impairment)	The group of patients with liver disease included in clinical studies with Ionsys was limited to 30 patients. The group size is too small to guide safe and effective dosing for patients with this condition.
Use in patients with kidney problems (renal impairment)	Only 21 patients with kidney disease were included in clinical studies with Ionsys. The group size is too small to guide safe and effective dosing for patients with this condition.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Ionsys can be found on Ionsys' EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Ionsys' EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

Misuse / Abuse / Diversion / Addiction and Dependence; Medication errors (including accidental exposure); Difficulty breathing; Overdose; Device not working correctly or at all; Inadequate product disposal; Off-label use

Risk minimisation measure: Healthcare Provider Education Programme
Objective and rationale: To inform healthcare professionals how to handle and use the transdermal system and how to reduce the risk of medication errors.
Description: All healthcare professionals who are expected to prescribe, dispense or administer Ionsys will be provided with 'Ionsys Instructions for Use and Disposal' and education material (including a Healthcare Prescriber Checklist) which will contain information on the correct use of the transdermal system and its proper disposal, as well as information on the risks of misuse, abuse and overdose.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Prescriber survey	To evaluate prescriber awareness and understanding of important identified and potential risks with Ionsys	• Misuse/abuse/diversion/ addiction and dependence • Medication errors (including accidental exposure) • Respiratory depression • Overdose • Device malfunction/failure, including use during MRI,	Planned for 18 months after EU launch	Final survey report date to be determined.

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
		cardioversion, or defibrillation • Inadequate product disposal		

Studies which are a condition of the marketing authorisation

The above activity is not a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 11-2015.